FAMILIAL MEDITERRANEAN FEVER—AN UPDATE*

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By classical description, familial Mediterranean fever (FMF) is a rare disorder characterized by recurrent, unprovoked episodes of fever and serositis lasting one to two days, with rapid, spontaneous lysis to a symptom-free state. It is inherited as an autosomal recessive trait, and occurs primarily in ethnic groups from the Mediterranean basin. The serious complication of amyloidosis occurs in 20–30% of patients of some, but not all, ethnic cohorts. Tissue amyloid represents the deposition of fibrils of a non-immunoglobulin polypeptide fragment, so-called amyloid A (1). Amyloid A derives from an acute phase serum protein, SAA, which is secreted by the hepatocyte (2). The etiology of FMF is unknown.

The introduction of prophylactic colchicine therapy nearly 15 years ago (3) has substantially altered the clinical course of FMF. It has also facilitated a greater appreciation of a wider clinical spectrum of the natural disease. Correspondingly, basic research delineating the underlying mechanisms of the general inflammatory response, as well as observations made on specimens obtained from FMF patients, permit the formulation of a provisional model for the pathogenesis of FMF. This progress report will offer a brief overview of clinical and conceptual advances made in recent years.

From a clinical standpoint, 3 major revisions have occurred in our appreciation of FMF. First, attacks should no longer be regarded as inevitable, for they are easily controlled in the great majority of patients. Continuous prophylaxis with 1 to 3 colchicine tablets daily provides total or near-total protection against attacks in 70% of patients and substantial benefit in another 20%. Except for mild diarrhea, the treatment is remarkably free of any significant side effects, even with long-term use (4). Second, colchicine also appears to protect against the development of amyloidosis. The suggestion that this might be the case has been made for some time by Israeli colleagues, and their published observations fully support earlier impressions (5). A large group of patients were followed for 4–11 years after being advised to take colchicine to prevent FMF attacks. Proteinuria was selected as the marker of amyloid nephropathy, a challengeable decision but not an unreasonable one in the context of

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the study. Of 960 patients who began treatment without proteinuria, 906 took the drug faithfully. In this group, only 1.7% developed proteinuria over 9 years. In contrast, proteinuria occurred in 49% of a smaller group of 54 non-compliant patients.

A third revision mandated in our clinical perception of FMF is that its clinical spectrum is broader than the classical description and diagnostic criteria earlier advanced by Israeli observers (6). To some extent, colchicine-responsiveness has enabled a greater sense of diagnostic confidence in previously indeterminate cases. In the U.S., as compared to Israel, Jews with FMF are very often of Ashkenazi and not Sephardic ancestry. Patients in the USA rarely describe synovitis or an erysipeloid rash, which are reported to occur in 75% and 40%, respectively, among Israelis with FMF. Most important, amyloidosis is extremely rare in the USA, a fact worth stressing to newly-diagnosed patients who tend to check things out in older textbooks that may not make this distinction. Patients with a clear clinical picture of FMF occasionally have no traceable ancestral link to the Mediterranean basin—an Oriental, a Nordic, or a person of Scotch-Cherokee origin, for example. The very term familial Mediterranean fever may serve as a deterrent to the clinician challenged to make the correct diagnosis in the atypical case, such as the patient with minimal fever and non-suggestive ancestry.

Still to be defined is the relationship of FMF to a newly recognized syndrome, hyperimmunoglobulinemia D and periodic fever, which was reported from The Netherlands 2 years ago (7). None of the 6 Dutch patients described were of Mediterranean extraction. Their disease resembled typical FMF in many ways: recurrent bouts of fever without evident cause, leukocytosis, colchicine responsiveness, and a positive family history, which included amyloidosis, in 3 instances. These patients differed from those with typical FMF, though, because headache and lymphadenopathy were prominent components of their attacks, rather than serositis, and all showed elevated serum levels of IgD. The relationship of the clinical presentation to the IgD abnormality is entirely speculative.

Consideration of the pathogenesis of FMF must inevitably focus upon the inflammatory process. It has long been known that the neutrophil is the dominant cell in FMF serositis, and in at least one study, enhanced chemotaxis was detectable in a Boyden chamber during acute attacks (8). Matzner and Brzezinski have recently reported a deficiency of an inhibitor to the chemotactic activity of the complement fragment C5a in joint and peritoneal fluid of FMF patients (9). As compared to normal controls whose peritoneal fluid (obtained at laparoscopy) produced 70% inhibition of C5a, FMF patients showed, on average, 7% inhibition. Because C5a is an extremely potent chemotactic agent, any deficiency of

its inhibitor could have an important amplifying, but not an initiating, role in an FMF attack. Aisen and coworkers have shown that FMF sera has increased neutrophilic aggregating activity (10). This property remains in lipid extracts of the sera which contain lipoxygenase pathway products, including 5-HETE and di-HETE, hydroxy fatty acids which are putative mediators of acute inflammation. Of interest, colchicine has been shown to block neutrophil production of HETE and leukotriene B4 *in vitro*. In work directed at the mononuclear limb of inflammation, Ilfeld and Kuperman have examined mononuclear suppressor cells in FMF. They found that such cells function poorly in inhibiting the proliferation of PHA-stimulated responder cells. Suppressor cell function could be restored by adding colchicine, *in vitro* or *in vivo* (11).

One other line of investigation that warrants emphasis is the identification of SAA protein, the precursor of FMF amyloid, as a secretory product of the hepatocyte. It appears to be an acute phase reactant, much like haptoglobin. ceruloplasmin, and fibrinogen. In mice, hepatocyte secretion of SAA can be stimulated by injection of casein, and this secretion is blocked by colchicine administration (2).

Interleukin-1 (IL-1) would have a predictable central role in any proposed schema of a disease such as FMF. It is released by the phagocytic monocyte in response to a variety of stimuli, and then serves to trigger a series of events associated with inflammation. Depending on what it is doing, IL-1 goes by a variety of other names including *endogenous pyrogen* to designate its fever producing effect upon the hypothalamus, *neutrophil activating factor* for its role in stimulating the polymorphonuclear reaction, *lymphocyte activating factor* for its stimulation of T and B cell proliferation, and *SAA-stimulating factor* to describe its action on the hepatocyte (12).

These various activities can be incorporated into a preliminary model for the pathogenesis of FMF, as shown in Figure 1. A question mark at the beginning is unavoidable. It expresses our complete ignorance of what the initiating event or events of an FMF attack might be. However, assuming that the monocyte is activated to release IL-1 early on, one can then consider the obvious triad of inflammation, fever, and the amyloid pathway. Within the inflammatory limb of the diagram are two findings: the deficiency of C5a inhibitor in FMF patients and the identification of lipoxygenase products in FMF fluids, both of which would augment neutrophil recruitment. The presence of leukotrienes would also modulate capillary permeability, vasodilation, and pain transmission. The role of lymphocytes in the FMF attack is less clear, but it is included because of the intriguing finding of suppressor cell dysfunction.

The amyloid pathway portrays the binding of secreted SAA peptide to HDL by a P protein before its degradation to fragments by a serine

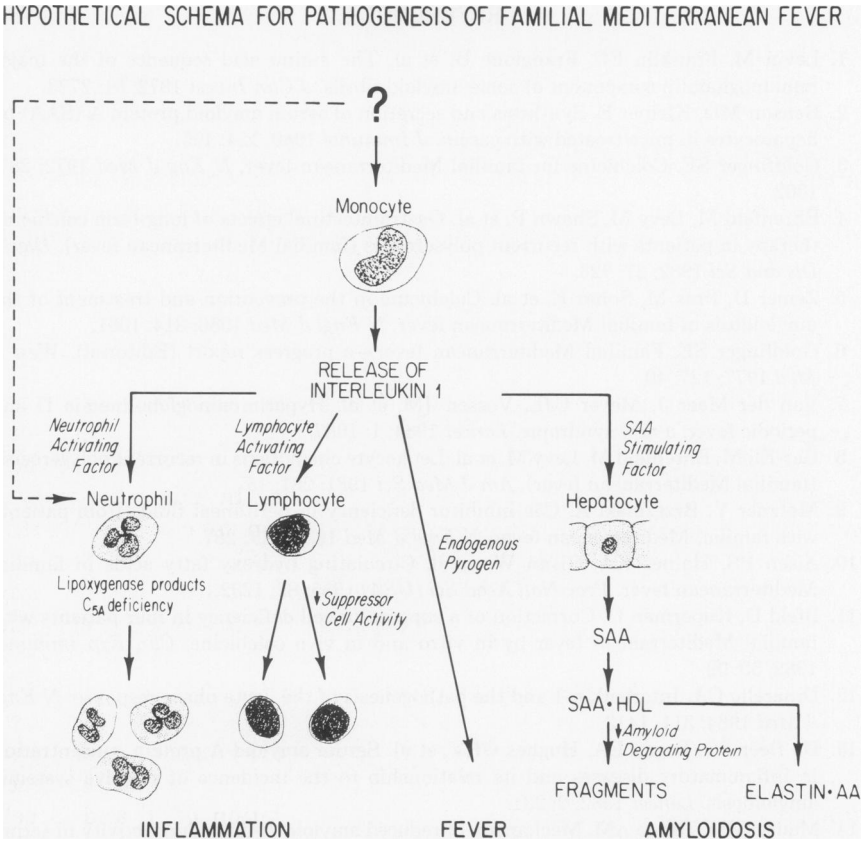

FIG. 1. A hypothetical schema for the pathogenesis of familial Mediterranean fever.

protease in the serum. It is possible that this protease is deficient in patients with FMF amyloidosis, as has been proposed in respect to amyloidosis secondary to rheumatoid arthritis (14). If so, such a deficiency would favor the deposition of amyloid fibrils into tissue.

Of interest in this hypothetical model is that there are 3 potential sites for colchicine suppression. The first is on the neutrophilic pathway, where colchicine has been shown to inhibit chemotaxis and suppress leukotriene release by white cells. The second is on the lymphocytic limb, by restoring suppressor cell function as proposed by Ilfeld and Kuperman (11). The third, of course, is through inhibiting the secretion of SAA protein by the stimulated hepatocyte.

This model is not intended to be a final statement. Rather, it is offered to invite challenge and modification. It is reasonable to expect that within the next decade, the scientific elucidation of the inflammatory process will reduce the mystery of FMF.

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DISCUSSION

Gray (Stanford): Steve, that was a lovely demonstration. I can't help but ask where's the Interleukin I? Is it found to be elevated in extracellular fluids or in tissues or serum of patients when they have attacks, or between attacks, or hasn't it been found at all?

Goldfinger: To my knowledge Interleukin I has not been measurable in body fluids. If that does become possible, I think we will learn a great deal.

Douglas (NY): Steve, I was—particularly as you related the story about the Dutch disease—intrigued to ask the old question again about the originating event, and it's still possible, as many thought in the beginning, that this is an infectious disease perhaps with a genetic predisposition. In the last 10 years we've learned a lot about how to grow new bacteria and new viruses, such as legionella species, borrelia species, retroviruses, etc. and I wonder what's been done in the effort to elucidate the originating cause?

Goldfinger: There's either been a great deal of negative results or no results at all, but certainly there's not been any reporting. And I don't know of any groups that are actively examining FMF fluids. There is an interesting side effect of the colchicine story. It has suppressed the opportunity to perform research on patients during the active phase of their disease. There are very few who are willing to forgo their colchicine to develop the

spontaneous attack that the researcher would like to have. In response to your question, I know of no effort to grow newer microorganisms in FMF patients.

Schreiner (D.C.): Patients who have been on hemodialysis for 7 years and beyond are showing a cumulative risk with time for the development of carpal tunnel syndrome and arthropathies and many of these have been histologically proven to represent amyloid deposition in those areas. And increasingly the nephrologists are using beta microglobulin as a marker for the events that can follow exposure of the blood to membranes—particularly of the cellulosic variety that have a propensity for triggering the complement cascade. They produce transient leukopenias and fever at the onset of dialysis and for the pulmonary sequestration of polys and therefore the release of substances like Interleukin and other bradykinins from the sequestration that occurs in the lung in dialysis patients. My question is, in your scholarship, which is excellent on this disease, have you come across any studies using betamicroglobulin in blood or urine as a marker or predictor for which patients are going to develop amyloidosis and are there any studies to show the effect of colchicine on such excretions?

Goldfinger: I have not. I do know that in Israel where amyloid was a major problem, the screening is all with simple urinary determination of protein and so I'm afraid I'd have to answer your question in the negative.

Maynard (Boston): Steve, that was a lovely depiction of a disease to which you've made major contributions in the understanding. I would like to shift to a very simple, practical management question that comes to those of us who take care of young people with this disease, and who are concerned about the genetic impact of long-term colchicine on their reproductive state. Is there sufficient experience to date to give full assurance to patients that low dose colchicine does not have any genetic impact?

Goldfinger: When it comes to advising the pregnant mother or the one wishing to become pregnant, it's very hard to deal in absolutes. There's always minimal risk, but probably not much more. In the Israel experience of 21 pregnancies on colchicine, there was one offspring with Down's Syndrome and 20 normal products of conception. It is my practice still to advise women to stop colchicine three months before planned conception. Why three months is selected and whether that is the best way of doing it I would not wish to defend. But interestingly, there are many people who, during those three months, have so many severe attacks they just can't stay off colchicine. I think it is very appropriate, of course, in the patient who becomes pregnant while taking 1 or 2 pills a day, to have an amniocentesis to check for Down's Syndrome. The time when you want the colchicine the most—the first trimester of pregnancy—is of course the time of greatest risk for fetal maldevelopment. Later on in pregnancy, the natural disease tends to ameliorate.

Calkins (Buffalo): It's really a joy to hear this nice presentation and to find that amyloid is still the subject of some interest in the Clinical and Climatological Association. Two questions. One is, with the hyperimmune globulin D type of amyloid, is that SAA type amyloid, or what type of amyloid is produced?

Goldfinger: That's an excellent question, Evan. In the article there was merely reference to several family members with amyloidosis, and you would expect on the one hand, if due to an immunoglobulin dyscrasia, that this would be the light chain amyloid which FMF patients don't have.

Calkins: Well, if it's light chain amyloid it would be a considerable reinforcement for the idea that colchicine might have some potential for the immunoglobulin type of amyloid which is still I think way up in the air.

Goldfinger: It is my understanding that the colchicine doesn't have an effect on the light chain amyloid, only on the SAA amyloid.

Calkins: The other thing is that the theory has been that given the fact that some patients will get the amyloid without the febrile involvement, and others the other way

around, there may be two genetically related but not identical syndromes. That perhaps, with the colchicine experience is no longer held. Maybe Victor or somebody can elucidate that for us. And what is your comment from your hypothesis about the fact that some patients will get the one and some the other?

Goldfinger: Another excellent question, Evan. I was expecting that one from someone who knew this disease. In the early reports of FMF, the Israelis did describe a phenotype type 2, a few patients who seemed to develop amyloid without attacks of FMF. That would prevent this unifying approach, with amyloid being an acute phase reactant. There were very few members of phenotype 2 group. In speaking with another group of Israelis—those at Jerusalem and not the Tel Hashauer Hospital—I learned it was their sense that amyloid did correlate with acute attacks. It also correlated, interestingly, with a Sephardic ancestry, and with synovitis.

Christy (Brooklyn): In regard to Dr. Calkin's remarks, I think the Climatological had better stay interested in amyloidosis since it's a disease of aging; but that isn't my question. I wanted to ask you, Dr. Goldfinger, the following: As I remember, colchicine does something bad to the metaphase stage of mitosis. I thought Dr. Maynard's question was more directed at teratogenesis. Is anything known about possible effects of colchicine over the long pull on gametogenesis?

Goldfinger: Very large doses or overdoses of colchicine will at least have a transitory effect upon cell division and proliferation if one were to examine appropriate tissue. At the level of one or two pills a day, the action is virtually unappreciable, clinically. In fact, I have a question for anyone who can answer it. If we postulate that colchicine has some fundamental effect upon tubulin, or upon suppressing polymorphonuclear function, why does it work so well for this disease and gout, and for rather little else? Why do patients on colchicine have no decrease in their normal resistance to various types of infection that require the neutrophil response? That's always puzzled me, and I've never had a good answer from neutrophil experts. It seems to be so specific that we feel it has some fundamental effect upon the neutrophil and yet neutrophil function remains intact when it is called upon to do its job in respect to other challenges.